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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/636,530	08/10/2000	Thomas L. Cantor	532212000300	7117

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Peng Chen
Morrison & Foerster
3811 Valley Centre Drive
Suite 500
San Diego, CA 92130-2332

EXAMINER	
JIANG, DONG	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/636,530	CANTOR, THOMAS L.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,16,39 and 41-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14, 16, 39, and 41-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

KD

DETAILED OFFICE ACTION

Applicant's amendment filed on 16 December 2004 is acknowledged and entered. Following the amendment, claim 40 is canceled, and claims 14, 39, 47 and 48 are amended.

Currently, claims 14, 16, 39, and 41-48 are pending and under consideration.

Withdrawal of Objections and Rejections:

All objections and rejections of claim 40 are moot as the applicant has canceled the claim.

The enablement rejection of claims 39-48 under 35 U.S.C. 112, first paragraph is withdrawn in view of applicant's amendment.

The prior art rejection of claim 14 under 35 U.S.C. 102(b) as being anticipated by Born et al. (Endocrinology, 1988, 123(4): 1848-53) is withdrawn in view of applicant's amendment.

Formal Matters:

Priority

Applicant's amendment to the specification filed on 06 July 2004 is acknowledged, which indicates that the present application claims benefit of provisional application 60/224,447, filed on August 10, 2002, and will be entered accordingly. It is noted that the filing date of 60/224,447 application is the same as that of the instant application.

Rejections under 35 U.S.C. §101 and §112:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 48 remains rejected under 35 U.S.C. 101 because the disclosed invention is inoperative and therefore lacks utility, for the reasons of record set forth in the last Office Action mailed on 13 September 2004, at pages 2-3.

Applicants argument filed on 16 December 2004 has been fully considered, but is not deemed persuasive for reasons below.

At pages 6-7 of the response, the applicant argues that while the Divieti reference is not prior art, it may be informative of the technical feasibility or operability of the claims, that it does not demonstrate that even PHT-(7-84) fails to bind to all PTH receptor, and it does not demonstrate that binding to PTH1R fails to occur at some biologically relevant concentration. This argument is not persuasive for the following reasons. First, the instant rejection is not a prior art rejection. Second, the prior art demonstrates that PHT-(7-84) acts via receptors *distinct* from the PTH1R, and indicates that the results shown are fully consistent with that PHT-(7-84) may exert unique *PTH1R-independent* antiresorptive effect by activating CPTHRs expressed in bone cells, where PTH1R is also expressed. Further, as additional supporting evidence, Divieti teaches, citing the prior art, that PHT-(7-84) inhibits the calcemic actions of PHT-(1-84) and PHT-(1-34) at doses much lower than would be predicted to effectively antagonize either form at the PTH1R, suggesting that CPTH fragments might act upon bone cells via mechanisms independent of the PTH1R *per se* (page 171, the second paragraph of the right column). Applicants, on the other hand, instead of focusing on what the prior teaches, merely argue what the prior art does not teach. Such argument, and argument only is not sufficient in the absence of any evidence to the contrary because the prior art demonstrates that PHT-(7-84) acts via receptors *distinct* from the PTH1.

Applicants further argue, at page 7 of the response, that it is generally known that the PTH receptor binding region falls within a region towards the C-terminus of PTH (1-38), and that residues 24-31 have been shown to contribute to the receptor interaction, and that accordingly the PTH antagonists used in claim 48 contain the sequences for binding to PTH1R and *would* be able to block PTH binding. This argument is not persuasive because Divieti's PTH antagonist is PHT-(7-84), which encompasses residues 24-31, and *is shown* to bind distinct receptors independent of the PTH1R.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 39 and 41-48 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 39 remains indefinite for the new recitation of "diagnosed with *excessive* PTH activity". The word "excessive" is a relative term, and is not defined by the claim, the specification does not provide a standard or boundaries for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what are the boundaries for "excessive PTH activity", and therefore, the metes and bounds of the claim cannot be determined.

The remaining claims are rejected for depending from an indefinite claim.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 39, 41, 42, 44 and 47 remain rejected under 35 U.S.C. 102(b) as being anticipated by Fukuda, EP 0 528 271 A1, for the reasons of record set forth in the last Office Action mailed on 13 September 2004, at page 5.

Applicants argument filed on 16 December 2004 has been fully considered, but is not deemed persuasive for reasons below.

At page 10 of the response, the applicant argues that claim 39 requires the use of a PTH antagonist, and Fukuda does not disclose the use of a PTH antagonist that counters the effect of PTH, that Fukuda discloses a PTH mutein comprising at least one of three types of modifications (N-terminal deletion of 3 to 6 residues, substitution of another residue for a methionine, and substitution for a cysteine within residues 34 to 47 (note: no cysteine in this region in hPTH) without teaching whether the antagonizing effect of it mutants are from the N-terminal deletion or from the other modifications, nor does Fukuda clarify the meaning of PTH antagonist. This argument is not persuasive for the following reasons. With respect to the use of a PTH

antagonist, as pointed by applicants, Fukuda clearly states that "the human PTH antagonist derivatives can be used as therapeutic agents for hepercalcemia and hyperparathyroidism" (page 9, lines 19-20). The later reads on a subject with excessive PTH activity (present claim 39), and thus, "reducing a catabolic effect of a PTH" would be inherent in the teachings by Fukuda. Further, with respect to whether the antagonizing effect of the mutants are from the N-terminal deletion or from the other modifications, Fukuda clearly states that "the present invention provides antagonists in which several amino acid residues on the N-terminal side of hPTH containing the C-terminal peptide chain are deleted (page 3, lines 12-13), and that "*in accordance with the present invention*, there are provide (1) a hPTH mutein comprising ..." (the three modifications). Therefore, each of the three specified modifications would produce PHT antagonist. However, regardless what the other modification had produced, the relevant issue here is that Fukuda clearly teaches that the N-terminal deletion results in PHT antagonist. Furthermore, with respect to the meaning of PTH antagonist, the meaning of "antagonist" is well established in the art, and silence about something well known and established in the art does not make the prior art non-anticipatory because one of ordinary skill in the art would understand the meaning of the term.

At page 11 of the response, the applicant argues that in other places of the reference, Fukuda teaches that the N-terminal deletions, e.g., hPHT(7-84), have agonist activity (page 23, lines 20-45), and that Fukuda's $PHT_{7-84}([Leu^8])$ is as active as hPTH, and thus, Fukuda actually teaches that PHT_{7-84} has the agonist activity. This argument is not persuasive because Fukuda does not teach so. At page 23 of the reference, Fukuda shows in the table the test result for muteins including "[Leu^8] human PTH", which is a mutein with an amino acid substitution at position 8, and does not have the N-terminal deletion. Fukuda's "[Leu^8] human PTH" is simply not $PHT_{7-84}([Leu^8])$ suggested by applicants.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 16 remains rejected and claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Takasu et al. (Endocrinology, 1996, 137(12): 5537-43), and Fukuda, EP 0 528 271 A1, for the reasons of record set forth in the last Office Action mailed on 13 September 2004, at page 6.

Applicants argument filed on 16 December 2004 has been fully considered, but is not deemed persuasive for reasons below.

At pages 12-13 of the response, the applicant argues that to establish an obviousness rejection, the Office must show, among others, that the references provide all of the limitations of the claimed invention, and that Takasu and Fukuda, individually or in combination, do not teach or suggest a PTH antagonist from PTH_{28-84} to PTH_{34-84} (as claim 16). This argument is not persuasive because, as addressed in the last Office Action, Fukuda teaches hPHT antagonist comprising the N-terminal deletions of 3 to 6 residues, and Takasu teaches a hPHT antagonist with minimum size of the fragment hPTH(35-84). Based on the combination teachings of the two references, it is instant obvious to a person having ordinary skill in the art that deletions within the range of residues 3 to 34 would be expected to be PHT antagonists. The presently claimed PHT antagonists of PTH_{9-84} (claim 14), PTH_{28-84} and PTH_{34-84} (as claim 16) fall within this range, therefore, are obvious over the cited prior art.

Claim 43 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Fukuda, EP 0 528 271 A1, as applied to claims 39, 41, 42, 44 and 47 above, for the reasons of record set forth in the last Office Action mailed on 13 September 2004, at page 7, and for the reasons above.

Claims 45 and 46 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Fukuda, EP 0 528 271 A1, as applied to claims 39, 41-44 and 47 above, and further in view of Kanmera et al., EP 0 451 867, for the reasons of record set forth in the last Office Action mailed on 13 September 2004, at pages 7-8.

Applicants argument filed on 16 December 2004 has been fully considered, but is not deemed persuasive for reasons below.

At pages 13-14 of the response, the applicant repeatedly argues that Fukuda does not teach or suggest the use of a PTH antagonist that counters the effect of PTH, and Kanmera does not cure the defect of Fukuda, and that the real PTH antagonists taught by Kanmera are derived from PTHrP. This argument is not persuasive because, as addressed in the last Office Action and above, Fukuda clearly and specifically teaches the use of a PTH antagonist as that "the human PTH antagonist derivatives can be used as therapeutic agents for hepercalcemia and hyperparathyroidism". Further, regardless what else Kanmera has taught in the reference, the relevant teaching is that the derivatives exhibit a potent inhibitory activity against hPTH are useful as a therapeutic agent for treating dysbolism associated with calcium or phosphoric acid, such as osteoporosis and renal osteodystrophy. Therefore, it is obvious from the combined teachings that Fukuda's PTH antagonists would be useful for treating osteoporosis and renal osteodystrophy.

Conclusion:

No claim is allowed.

Advisory Information:

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

Dong Jiang, Ph.D.
Patent Examiner
AU1646
4/14/05